CASE TN0017 NP

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

IN RE APPLICATION OF
ABRAMOWITZ ET AL.
APPLICATION NO: 09/821,103 EXAMINER: HOWARD V. OWENS, JR.
FILED: MARCH 29, 2001 ART UNIT: 1623
FOR: SUSTAINED RELEASE BEADLETS CONTAINING STAVUDINE

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**APPEAL BRIEF PURSUANT TO 37 CFR §1.192**

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Sir:

This brief is submitted, under 37 CFR 1.192 following the Notice of Appeal filed January 13, 2005. The fee for submission of this brief may be charged to deposit account no. 19-3880 (extra copy of brief enclosed).

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(1) **REAL PARTY IN INTEREST**

The real party in interest in this appeal is Bristol-Myers Squibb Company, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000. Bristol-Myers Squibb Company is the assignee and owner of the entire interest in the above-identified application by virtue of an assignment which was recorded in the United States Patent and Trademark Office on April 26, 2001 at Reel/Frame 011752/0746.

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(2) **RELATED APPEALS AND INTERFERENCES**

Appellants are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) **STATUS OF CLAIMS**

Claims 1-25 are pending in this appeal. A clean copy of the claims is provided in Appendix A.

(4) **STATUS OF AMENDMENTS**

No Amendments have been filed subsequent to the Final Rejection dated October 20, 2004.

(5) **SUMMARY OF CLAIMED SUBJECT MATTER**

In the treatment of HIV infection, it is common for patients to have a very large daily pill burden. A reduced pill burden may result in increased patient adherence to their HIV regimens, particularly for the drugs for which a once daily dosing can be implemented. Once daily dosing is important in terms of achieving enhanced patient compliance, improved sustained blood levels of medication, safety, and patient convenience.

Stavudine is a nucleoside reverse transcriptase inhibitor which is effective in the treatment of infections caused by retroviruses such as human immunodeficiency virus (HIV). While stavudine would be amenable to once daily dosing if a suitable extended release formulation could be developed, a problem in the formulation of a suitable extended dosage form is its sensitivity to moisture that causes it to hydrolyze, primarily into thymine. Once stavudine has degraded to thymine it loses its effectiveness.

The present invention provides a solution to the degradation problem. The beadlets are suitable for preparing extended release dosage forms capable of providing 24 hour blood levels of stavudine with a single dose. A further advantage to the beadlet of the present invention is that it is possible to combine two or more medications individually into the beadlets, which are then filled into conventional hard gelatin capsules. This avoids any potential compounding problems that might be encountered with trying to combine such medications into the same formulation.

The beadlets of the present invention include an amount of magnesium stearate sufficient to stabilize stavudine against degradation during the extrusion-spheronization process used to form

the beadlets. Also included in the beadlets is a spheronizing agent. In a specific embodiment, the beadlets also contain a diluent. After formation and drying, the beadlets are coated with a seal coating utilizing conventional film formers in combination with an antiadherent agent to retard the tendency of the beadlets to agglomerate during the coating operation. The beadlets are then coated with a barrier or modified release coating to achieve extended dissolution and absorption over a period such that they will provide blood levels of stavudine over a 24 hour period. The modified release coating comprises a polymeric barrier material and a suitable plasticizer therefore.

## (6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1-25 are obvious under 35 USC § 103(a) over the combined teachings of Lin et al. (U.S. Patent No. 4,978,655) and Ullah et al (U.S. Patent No. 6,607,747).

## (7) GROUPING OF CLAIMS

The claims on appeal do not stand or fall together. The claims are believed to have the following grouping:

Group A, claims 1-14; claim 26
Group B, claim 21
Group C, claims 15-20;
Group D, claims 22-25 and 27-30; and
Group E, claims 31-34.

The reasons why the claims of the groups are believed to be separately patentable are set forth in the Argument section of this Appeal Brief.

## (8) ARGUMENT

### Ullah et al. (U.S. Patent No. 6,607,747) Not Eligible as a Reference

The Examiner's position with respect to the eligibility of U.S. Patent 6,607,747 as prior art, as set forth on page 2 of the Final Rejection, is as follows:

> Applicant has provided evidence in this file showing that the invention was owned by, or subject to

> an obligation of assignment to, the same entity as 6,607,747 at the time this invention was made. Accordingly, 6,607,747 is disqualified as prior art through 35 U.S.C. 102(f) or (g) in any rejection under 35 U.S.C. 103(a) in this application. However, this applied art additionally qualifies as prior art under another subsection of 35 U.S.C. 102, 102(e) and accordingly is not disqualified as prior art under 35 U.S.C. 103(a). (underline added)

However, 35 USC § 103(c), as amended on November 29, 1999, reads:

> (c) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This change to 35 USC § 103(c) applies to all utility, design, and plant patent applications filed on or after November 29, 1999 and thus applies to the subject patent application which was filed on March 29, 2001. Thus, it is respectfully submitted that the Examiner's assertion is incorrect. U.S. Patent No. 6,607,747 and the subject patent application are both owned by Bristol-Myers Squibb Company. Thus, Appellants respectfully submit that according to 35 USC § 103(c), U.S. Patent No. 6,607,747 is not eligible as prior art. Note that the assignments for the subject patent application and the reference can be found at reel/frame numbers 011752/0746 and 9317/0197, respectively.

Accordingly, as both U.S. Patent 6,607,747 and the subject patent application were subject to an obligation of assignment to Bristol-Myers Squibb Company, it is Appellants' position that U.S. Patent 6,607,747 is not eligible as a reference.

Without U.S. Patent 6,607,747 the *prima facie* case cannot be sustained. As noted by the Examiner in page 3 of the Final Rejection:

> Lin however does not specifically teach an extruded spheronized form nor the addition of didanosine.

Thus, even the U.S. Patent and Trademark Office admits that the primary reference is

insufficient to render Appellants' claims obvious. Therefore, Appellants respectfully submit that a *prima facie* case of obviousness cannot be made based on Lin et al., U.S. Patent No. 4,978,655 alone. It is therefore requested that the Examiner's rejection be reversed for all of the claim groupings (Groups A-D).

**Lin et al. (U.S. Patent No. 4,978,655) and Ullah et al. (U.S. Patent No. 6,607,747) Do Not Teach the Claimed Invention**

Even assuming for the sake of argument that U.S. Patent No. 6,607,747 would be eligible as a reference, the combination with U.S. Patent No. 4,978,655 would not support a *prima facie* case of obviousness for the reasons stated below.

The Examiner's position with respect to the applied references, as set forth on page 3 of the Final Rejection is as follows:

> Lin teaches the formation of stavudine (d4T) in a composition with common pharmaceutical excipients –such as magnesium stearate, carboxymethyl cellulose and cellulose derivatives, diluents, protective matrices and polymeric substances for sustained delivery (col. 4, lines 10-43). Lin however does not specifically teach an extruded spheronized form nor the addition of didanosine. Ullah adequately bridges the nexus between Lin and the instant claims as it teaches the use of a pharmaceutical composition comprising an extruded spheronized (beadlet) containing the claimed plasticizers, coatings and carboxymethylcellulose binders for stability and modification of the dissolution profile (as well as beadlet formation) wherein the medicament may comprise didanosine or like acid labile compounds (col. 2, line 35 – col. 5, line 12; see also col. 5, line 55 – col. 6, line 16).

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead individual to combine the relevant teachings of the references. Ex parte Obukowicz, 27 USPQ 2d 1063, 1065 (B.P.A.I. 1992).

"Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so." (quoting ACS Hosp. Systems, Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)). The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. In re Fritch, 972 F.2d 1260, 23 USPQ 2d 1780, 1783-1784 (Fed. Cir. 1992).

The Examiner has failed to show any teaching or suggestion in Lin et al. of the use of a quantity of magnesium stearate sufficient to stabilize moisture-sensitive medicaments in extended release formulations. Lin et al. disclose magnesium stearate as an example of a lubricant that can be used in pharmaceutical compositions adapted to be formed into tablets, dragees, capsules and pills. Lin provides no disclosure or suggestion that magnesium stearate can stabilize stavudine against degradation, let alone the quantities needed to achieve stabilization. The fact that the cited reference generally discloses the use of magnesium stearate as a lubricant does not detract from the patentability of Appellants' invention, i.e., the use of magnesium stearate to stabilize stavudine in an extended release formulation.

Moreover, Lin et al. equates both talc and magnesium stearate as having equivalent effectiveness as lubricants. However, Appellants have found that talc does not produce the stabilizing effect during the extrusion process provided by magnesium stearate. As stated on page 6, lines 9-16 of Appellants' specification,

> Magnesium stearate is effective in stabilizing stavudine in the granulation whereas other similar conventional tabletting lubricants/processing aids, such as talc and colloidal amorphous silicon, do not produce the stabilizing effect.

As talc does not produce the stabilizing effect that is demonstrated by magnesium stearate, Lin's suggestion that talc and magnesium stearate are equivalent teaches away from Appellants' invention.

For the foregoing reasons Appellants submit that Lin et al. does not teach or suggest Appellants' invention, which is the use of magnesium stearate to stabilize stavudine in an extended release formulation.

As such, the Examiner cites Ullah et al. to compensate for the shortcomings of the primary reference. As with Lin et. al, the Examiner has failed to show any teaching or suggestion in Ullah et al. of the use of magnesium stearate as a stabilizer for moisture-sensitive medicaments. Ullah et al. disclose the formation of extended release beadlets of acid-sensitive medicaments such as didanosine. As stated in column 3, lines 14-18 of the reference,

> A granulation solvent, such as is typically suitable for spheronization of an acid labile medicament, is mixed with (a) an acid labile medicament, (b) optionally a binder, and (c) optionally a disintegrant, to form a wet mass. The preferred granulation solvent is water.

There is no suggestion or teaching of how to form extended release beadlets containing both didanosine and stavudine, nor is there any suggestion or teaching of the use of magnesium stearate as a stabilizer for moisture-sensitive medicaments in an extended release formulation.

As neither Lin et al. nor Ullah et al. teach or suggest the use of magnesium stearate as a stabilizer for stavudine or other moisture-sensitive compounds, it is Appellants' position that the references, either alone or in combination, are insufficient to render the claims of Group A, claims 1-14, which recite extruded-spheronized beadlets comprising stavudine, a spheronizing agent, and a quantity of magnesium stearate sufficient to stabilize stavudine against degradation during the extrusion-spheronization process, obvious.

In addition, neither Lin nor Ullah teach or suggest that magnesium stearate can solve the problem solved by Appellants in claim 21 of Group B, e.g., making an extended release formulation that contains a quantity of magnesium stearate sufficient for stabilizing stavudine and provides an effective dosage of stavudine over approximately 24 hours. Thus, it is Appellants' position that the references, either alone or in combination, are insufficient to render the claim of Group B obvious.

The claims of Group C recite extended-spheronized beadlets comprising stavudine, a spheronizing agent, a diluent, magnesium stearate in an amount sufficient to stabilize stavudine against degradation during the extrusion-spheronization process, a seal coating, and a modified release coating. As neither Lin et al. nor Ullah et al. teach or suggest the combination of the six ingredients recited in independent claim 15 and dependent claims 16-20 or the use of magnesium stearate as a stabilizer for stavudine or other moisture-sensitive compounds, it is Appellants'

position that the references, either alone or in combination, are insufficient to render the claims of Group C obvious.

The claims of Group D recite pharmaceutical dosage forms comprising a hard gelatin capsule containing the extruded-spheronized beadlets of the present invention and additionally at least one other medicament useful in treating retroviral infections as well as methods of treating patients using these dosage forms. The Examiner has failed to show any teaching or suggestion in the cited references of a pharmaceutical dosage form comprising stavudine, another retroviral medicament, and a sufficient quantity of magnesium stearate to provide an effective dosage of stavudine and a blood level of the other retroviral medicament over approximately 24 hours or of methods of using these dosage forms. Thus, Appellants submit that the references are insufficient to render claims 22-25 and claims 27-30 obvious.

A process of forming beadlets containing stavudine is recited in the claims of Group E. The process comprises forming a wet mass of stavudine, a spheronizing agent, an optional diluent, an amount of magnesium stearate sufficient to stabilize the stavudine against degradation during said process, and water sufficient to form a wet mass suitable for extrusion; extruding said mass to form an extrudate; spheronizing said extrudate to form beadlets; and drying said beadlets. As the Examiner has failed to show any teaching or suggestion in the cited references of the process steps recited in independent claim 31 and dependent claims 32-34, it is Appellants' position that the references, either alone or in combination, are insufficient to render the claims of Group E obvious.

Thus, for the foregoing reasons, it is submitted that the Examiner has failed to establish a *prima facie* case of obviousness over Appellants' claimed invention. Therefore, it is requested that the rejection under 35 USC § 103(a) for the claims of Groups A-E be withdrawn.

Respectfully submitted,

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## APPENDIX

## CLAIMS ON APPEAL

1. Extruded-spheronized beadlets comprising stavudine, a spheronizing agent, and a quantity of magnesium stearate sufficient to stabilize stavudine against degradation during the extrusion-spheronization process.

2. The beadlets of Claim 1 containing from about 0.5 to about 3.0 percent by weight of magnesium stearate based on the weight of stavudine present therein.

3. The beadlets of Claim 1 containing from about 1.4 to about 1.7 percent by weight of magnesium stearate based on the weight of stavudine present therein.

4. The beadlets of Claim 1 wherein the spheronizing agent is selected from the group consisting of microcrystalline cellulose, sodium carboxymethyl cellulose and corn starch.

5. The beadlets in Claim 4 wherein the spheronizing agent is microcrystalline cellulose.

6. The beadlets of Claim 1, further comprising a diluent.

7. The beadlets of Claim 6 wherein said diluent is selected from consisting of lactose, dicalcium phosphate, mannitol and cornstarch.

8. The beadlets of Claim 1, further comprising a seal coating and a modified release coating.

9. The beadlets of Claim 8 wherein the seal coating comprises a film-former and an antiadherent, and the modified release coating comprises a polymeric barrier material and a plasticizer therefor.

10. The beadlets of Claim 9 wherein the film-former is selected from the group consisting of hydroxypropyl methylcellulose and hydroxypropyl cellulose.

11. The beadlets of Claim 9 wherein the antiadherent is selected from the group consisting of talc, microcrystalline cellulose and magnesium stearate.

12. The beadlets of Claim 9 wherein the polymeric barrier material comprises polymethacrylate.

13. The beadlets of Claim 9 wherein the polymeric barrier material comprises ethylcellulose.

14. The beadlets of Claim 9 wherein the plasticizer comprises acylated monoglycerides.

15. Extended-sphereonized beadlets, comprising:

a) stavudine;

b) a spheronizing agent;

c) a diluent;

d) magnesium stearate in an amount sufficient to stabilize stavudine against degredation during the extrusion-spheronization process;

e) a seal coating; and

f) a modified release coating.

16. The beadlets of Claim 15 containing from about 33 to about 67 percent by weight of stavudine.

17. The beadlets of Claim 15 wherein the spheronizing agent is selected from the group consisting of microcrystalline cellulose, sodium carboxymethyl cellulose and corn starch.

18. The beadlets of Claim 15 wherein the diluent is selected from the group consisting of lactose, dicalcium phosphate, manitol and corn starch.

19. The beadlets of Claim 15 wherein

a) the spheronizng agent is microcrystalline cellulose;

b) the diluent is lactose;

c) the seal coating comprises a film-former and an antiadherent; and

d) the modified release coating comprisese a polymeric barrier material and a plasticizer.

20. The beadlets of Claim 19 wherein said film-former is hydroxypropyl methylcellulose, said antiadherent is talc, said polymeric barrier material is ethylcellulose and said plasticizer comprises distilled acetylated monoglycerides.

21. A pharmaceutical dosage form comprising a hard gelatin capsule containing a sufficient amount of the beadlets of Claim 1, 15 or 19 to provide an effective dosage of stavudine over approximately 24 hours.

22. The pharmaceutical dosage form of Claim 21, wherein said capsule additionally contains beadlets containing at least one other medicament useful in treating retroviral infections such that blood levels of said other medicament are provided over approximately 24 hours.

23. The pharmaceutical dosage form of Claim 22, wherein said other medicaments are selected from the group consisting of didanosine, [3S-(3R*,8R*,9R*,12R*)]-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6{[4-(2-pyridinyl)phenyl]methyl}-2,3,6,10,13-pentaazaretetradecanedioic acid dimethyl ester, indinavir and lodenosine.

24. The pharmaceutical dosage form of Claim 23 wherein said other medicament is didanosine.

25. The pharmaceutical dosage form of Claim 23 wherein said other medicament comprises

(a) [3S-(3R*,8R*,9R*,12R*)]-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6{[4-(2-pyridinyl)phenyl]methyl}-2,3,6,10,13-pentaazaretetradecanedioic acid dimethyl ester; and

(b) optionally didanosine.

26. A method of treating a patient in need of therapy for a retroviral infection comprising administering to said patient a pharmaceutical dosage form comprising a hard gelatin capsule containing a sufficient amount of the beadlets of Claim 1, 15 or 19 to provide an effective dosage of stavudine, thereby providing said treatment over approximately 24 hours.

27. The method of Claim 26 wherein said capsule additionally contains beadlets containing at least one other medicament useful in treating retroviral infections such that treatment with said other medicament is provided over approximately 24 hours.

28. The method of Claim 27 wherein said other medicament is selected from the group consisting of didanosine, [3S-(3R*,8R*,9R*,12R*)]-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6{[4-(2-pyridinyl)phenyl]methyl}-2,3,6,10,13-pentaazaretetradecanedioic acid dimethyl ester, indinavir and lodenosine.

29. The method of Claim 28 wherein said other medicament is at least one of didanosine and [3S-(3R*,8R*,9R*,12R*)]-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6{[4-(2-pyridinyl)phenyl]methyl}-2,3,6,10,13-pentaazaretetradecanedioic acid dimethyl ester.

30. The method of Claim 29 wherein said other medicament is didanosine.

31. A process of forming beadlets containing stavudine, comprising:

(a) forming a wet mass of stavudine, a spheronizing agent, an optional diluent, an amount of magnesium stearate sufficient to stabilize the stavudine against degradation during said process, and water sufficient to form a wet mass suitable for extrusion;

(b) extruding said mass to form an extrudate;

(c) spheronizing said extrudate to form beadlets; and

(d) drying said beadlets.

32. The process of Claim 31, further comprising the steps of forming a seal coating over said beadlets and forming a modified release coating over said seal coating.

33. The process of Claim 32 wherein said spheronizing agent is microcrystalline cellulose, said diluent is lactose, said seal coating comprises a film-former and an antiadherent, and said modified release coating comprises a polymeric barrier material and a plasticizer therefor.

34. The process of Claim 31, futher comprising the step of blending stavudine, the spheronizing agent, the optional diluent and magnesium stearate prior to forming the wet mass.